

REMARKS

The above amendments to the above-captioned application along with the following remarks are being submitted as a full and complete response to the Official Action (Paper No. 20050112) dated February 4, 2005. In view of the above amendments and the following remarks, the Examiner is respectfully requested to give due reconsideration to this application, to indicate the allowability of the claims, and to pass this case to issue.

Status of Claims

Claims 1-6 are pending in this application. Claims 17-12 have been withdrawn from further consideration as being directed to nonelected invention. Claims 1-6 stand rejected. Claims 1-2 and 5-6 have been amended to clarify the invention. Support for the recitation "couple with G-proteins other than Gq subtype G-proteins" can be found in the specification, for example, at page 8, lines 17-20. Support for the recitation "consisting of, from N-terminus to C-terminus, amino acid sequence of Gq α or G₁₁ α subunit N-terminal region encompassing $\beta\gamma$ subunit activation site and amino acid sequence of G₁₄ α , G₁₅ α , or G₁₆ α subunit C-terminal region encompassing receptor binding site" can be found, for example, in Figure 1. No new matter is added by these amendments.

Oath/Declaration

The Examiner notes on page 2 of the Office Action that "[a] new oath or declaration is required because the oath/declaration is written in Japanese and does not appear to coincide with the instant application. Applicants respectfully believe that a new oath or declaration is not required because it has used the declaration form (PTO/SB/106) suggested by the Patent Office and the declaration form signed by the inventors has names of the inventors and title of the invention, which title was on the specification as filed. A signed declaration, containing such information, filed on the application filing date with a specification is acceptable as complying with the requirements of 37 CFR § 1.63. See, MPEP §602.

Priority

Applicants gratefully acknowledge the Examiner's observations regarding the foreign priority document. Applicants will attend to the translation, as recommended by the Examiner, in due course.

IN THE DRAWINGS:

The attached sheet of drawing includes changes to Figure 7. This sheet replaces the original sheet containing Figure 7. In Figure 7, the typographic error "GENE TRANSFICTION" has been corrected. A Letter to the Draftsperson is submitted herewith.

Drawing Objections

On page 3 of the Office Action, the Examiner noted that “[t]he drawings are objected to because Fig. 7 contains the typographic error: ‘GENE TRANSFICTION’.” Applicants submit herewith a replacement sheet containing Fig. 7 and believes that it is in compliance with 37 CFR § 1.121.

Claim Objections

Claims 2, 5 and 6 are objected to because of certain informalities.

Specifically, the Examiner noted that claims 2 and 6 recite G_{11} and G_{14} where these molecules were previously recited as $G_{11}\alpha$ and $G_{14}\alpha$, respectively and claim 5 contains a typographic error: “subunitconstituted”. Applicants respectfully submit that these objections have been rendered moot in view of the amendments to claims 2, 5 and 6.

Rejections Under 35 U.S.C. §112

Enablement

Claims 1-6 stand rejected under 35 U.S.C. 112, first paragraph, based on the assertion that the specification, while being enabling for recombinant cells and methods of producing recombinant cells comprising known GPCRs and a chimeric $G\alpha$ subunit comprising specified regions of $G_{11}\alpha$ and $G_{14}\alpha$, does not reasonably provide enablement for recombinant cells and methods of producing recombinant cells comprising GPCRs, as broadly claimed, and a chimeric $G\alpha$ subunit comprising $G_{11}\alpha$ and $G_{14}\alpha$ wherein the $G\alpha$ subunit is constituted by a “portion of” $G_{11}\alpha$ and $G_{14}\alpha$.

Without conceding the validity of this rejection and solely to expedite the prosecution of this application, Applicants have elected to revise claims 1 and 5. To the extent the Examiner maintains that the pending claims, as amended, are not enabled, Applicants respectfully traverse.

As a preliminary matter, Applicants respectfully submit that the presence of both anticipation rejection and enablement rejection in the Office Action against the same claims appears contradictory. For example, the Examiner found Nakamura et al., 1996, J. Biochem., 120:996-1001, to be an anticipatory reference (discussed more fully below). This reference teaches *Xenopus* oocytes transfected with chimeric Gq subtype G-proteins together with metabotropic glutamate receptor subtype 1. To constitute an anticipatory reference, the prior art must contain an enabling disclosure. *Chester v. Miller*, 15 USPQ2d 1333 (Fed. Cir.

1990). If the Examiner believes that Nakamura anticipates the claims as originally filed, then Nakamura has disclosure sufficient to practice those claims, i.e., Nakamura enables the claims as originally filed. The specification need not disclose what is well-known to those skilled in the art. To the extent there is any missing information in the specification to practice the presently claimed invention, one skilled in the art could consult Nakamura and supply the missing information without undue experimentation.

Notwithstanding and turning to the issue of GPCRs encompassing orphan GPCRs, Applicants respectfully submit that "Orphan GPCRs are receptors with unknown functions." See, Lin et al. (Annals of Medicine, 2004, 36:204-214), at page 205, right column. In contrast, the GPCRs recited in the instant claims are those that couple with specific G-proteins, i.e., G-proteins other than Gq subtype G-proteins. Such GPCRs and G-proteins other than Gq subtype G-proteins are already known to one skilled in the art. For example, the H₂, M₂, M₄, and δ opioid receptors are among those that couple with G-proteins other than Gq subtype G-proteins (Gs or Gi subtype). See specification at page 8, lines 19-20. The genes encoding the GPCRs and G-proteins other than Gq subtype G-proteins can be prepared based on the published nucleic acid data. Given what is already known about GPCRs and G-proteins other than Gq subtype G-proteins, selecting a GPCR that couples with G-proteins other than Gq subtype G-proteins is within the purview of one skilled in the art and is not an inventive activity. Those skilled in the art would have successfully used any GPCR that couples with G-proteins other than Gq subtype G-proteins based on the disclosure in the application and the general knowledge available in the art.

With regard to chimeric Gq α subunit, Applicants respectfully submit that the subunit consists of, from N-terminus to C-terminus, amino acid sequence of Gq α or G₁₁ α subunit N-terminal region encompassing $\beta\gamma$ subunit activation site, and amino acid sequence of G₁₄ α , G₁₅ α , or G₁₆ α subunit C-terminal region encompassing receptor binding site. Figure 1 illustrates two such chimeric Gq α subunits. By employing calcium-dependent Cl current assay, Applicant has shown that H₂, M₂, M₄, and δ opioid receptors could induce responses when a chimeric Gq α subunit is coexpressed. When the G₁₁ α or the G₁₆ α subunit instead of the chimeric Gq α subunit is coexpressed, such effect is not obtained. See, for example, the working example disclosed at specification pages 7-8.

The Luck article (Luck et al., 1991, Molecular Endocrinology, 5:1880-1886) relied on by the Examiner is inapplicable because it does not concern chimeric proteins, much less

chimeric Gq α subunits. The subunits, Gq α , G₁₁ α , G₁₄ α , G₁₅ α and G₁₆ α are all well characterized proteins and their amino acid sequences are known in the art. All methods needed to make various chimeric Gq α subunits are also known in the art. Using these known methods, Applicant constructed the G₁₁ α /G₁₄ α chimeras expressed them. There was also a high level of skill in the art at the time the instant application was filed. A person skilled in this art would recognize that the disclosure in the specification as reasonably correlating to the full scope of the claimed invention and hence would have been able to make genes encoding a chimeric construct required by the instant claims by using only the teachings of the specification and the general knowledge available to such a person at the time that the application was filed. Applicants respectfully submit that the experimentation needed to construct chimeric Gq α subunits and to use those constructs would not be undue, since those can be determined by only routine and reasonable experimentation. Accordingly, reconsideration and withdrawal of the enablement rejection are respectfully requested.

Written Description

Claims 1-6 stand rejected under 35 U.S.C. § 112, first paragraph based on the assertion that these claims fail to comply with the written description requirement.

Specifically, the Examiner contends that claims 1-6, drawn to recombinant cells and methods of producing such recombinant cells consisting of GPCRs generically and the claims currently encompass a genus of receptors that are divergent in function. The Examiner also contends that the disclosure does not limit what constitutes a "portion of" G₁₁ α and G₁₄ α .

Without conceding the validity of this rejection and solely to expedite the prosecution of this application, Applicants have elected to revise claims 1 and 5. The revised claims recite GPCRs that couple with G-proteins other than Gq subtype G-proteins. The GPCRs include, for example, the H₂, M₂, M₄, and δ opioid receptors that couple with Gs or Gi subtype G-proteins. See specification at page 8, lines 19-20. Applicants respectfully submit that the specification does provide adequate written description of the claimed invention. Further, satisfaction of the written description requirement is measured by the understanding of one skilled in the art. Applicants respectfully submit that the use of GPCRs broadly in this invention would naturally occur to one skilled in the art upon reading the specification's explicit description of a generic invention and the description of representative GPCRs that couple with G-proteins other than Gq subtype G-proteins.

Accordingly, the specification describes the claimed invention in sufficient detail that one skilled in the art would reasonably conclude that the genus of GPCRs are properly within the subject matter which Applicants consider to be its invention and, therefore, the Applicants' invention includes the use of GPCRs broadly.

The written description issue with respect to the recitation, "portion of" is moot in view of the revised claims presented herein. The claims recite "a chimeric Gq α subunit consisting of, from N-terminus to C-terminus, amino acid sequence of Gq α or G₁₁ α subunit N-terminal region encompassing $\beta\gamma$ subunit activation site and amino acid sequence of G₁₄ α , G₁₅ α , or G₁₆ α subunit C-terminal region encompassing receptor binding site." One skilled in the art knows that a typical heterotrimeric G protein consists of an alpha subunit of three hundred and several dozen amino acids (full-length) and the alpha subunit in its N-terminal region has a $\beta\gamma$ subunit activation site and in its C-terminal region has a site for binding receptor proteins. This spatial relationship has been explicitly described in the specification (see, specification at page 3, lines 16-19) and illustrated in Figure 1. Applicants respectfully submit that these teachings are sufficient distinguishing characteristics of the chimeric Gq α subunit recited in the instant claims and are in sufficient detail that one skilled in the art can reasonably conclude that the inventors had possession of the claimed invention.

Accordingly, reconsideration and withdrawal of the written description rejection are respectfully requested.

Indefiniteness

Claims 2 and 6 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Specifically, the Examiner avers that "it is unclear as to what . . . would make up an 'N-terminal side' and a 'C-terminal side.'" Applicants respectfully submit that this rejection is moot in view of the revised claims presented herein.

Claims 5-6 also stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Specifically, the Examiner avers that the recitation of "group" makes the claim indefinite. Applicants respectfully submit that this rejection is moot in view of the revised claims presented herein.

Rejection Under 35 U.S.C. § 102

Claims 1-2 and 5-6 are rejected under 35 U.S.C. § 102(b) as being anticipated by Nakamura et al., 1996, J. Biochem., 120:996-1001. Applicants respectfully traverse this rejection for at least the following reasons.

A prior art reference anticipates a patent claim if the reference discloses, either expressly or inherently, all of the limitations of the claim. *Bristol-Myers Squibb v. Ben Venue*, 246 F.3d 1368 (Fed. Cir. 2001); *Schering Corporatin v. Geneva Pharmaceuticals, Inc.*, 339 F.3d 1373 (Fed. Cir. 2003); *See also, M.P.E.P. §2131 citing Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Absence from the reference of any claimed element negates anticipation. *Kloster Speedsteel AB v. Crucible, Inc.*, 230 USPQ 81 (Fed. Cir. 1986).

Nakamura teaches *Xenopus* oocytes transfected with chimeric Gq subtype G-proteins (i.e., chimeric G_{L1α}, a bovine version of G_{14α}, and G_{L2α}, a bovine version of G_{11α}) together with metabotropic glutamate receptor subtype 1 (mGluR1). Nakamura teaches specific chimeric constructs capable of coupling with mGluR1 and activate endogenous phospholipase C in the same manner as in G_{L2α} in response to glutamate stimulation.

Claims 1 and 5, as amended, require G-protein coupled receptors (GPCRs) that couple with G-proteins other than Gq subtype G-proteins. As exemplified in the Applicant's disclosure (see page 8, lines 17-22), the H₁, M₁, M₃, M₅, and mGlu1 GPCR receptors are among those that couple with G-proteins of the Gq subtype. The H₂, M₂, M₄, and δ opioid receptors are among those that couple with G-proteins other than Gq subtype G-proteins. The receptor used by Nakamura is one that couples with G_{L2α}, a Gq subtype G-protein. Nakamura does not teach or disclose cells transfected with chimeric Gq subtype G-proteins together with GPCRs that couple with G-proteins other than Gq subtype G-proteins. Because Nakamura fails to teach or disclose each and every limitation of claims 1 and 5, Nakamura cannot anticipate claims 1 and 5. The rejected dependent claims 2 and 6 by virtue of their dependency from the independent claim 1 or 5 are similarly considered by Applicants to patentably define themselves over the Nakamura reference. As such, claims 1-2 and 5-6 stand in condition for allowance for these very same reasons. Reconsideration and withdrawal of this rejection are respectfully requested.

Rejection Under 35 U.S.C. § 103

Claims 3-4 stand rejected under 35 U.S.C. § 103(b) as being unpatentable over

Nakamura et al., 1996, J. Biochem., 120:996-1001. Applicants respectfully traverse this rejection for at least the following reasons.

To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Nakamura is discussed above. Nakamura does not teach or suggest the features set forth in claims 3 and 4. For example, Nakamura does not teach or suggest GPCRs that couple with G-proteins other than Gq subtype G-proteins or cells expressing such GPCRs and chimeric Gq subtype G-proteins. If any thing, Nakamura teaches just the opposite, i.e., expression of GPCRs that couple with Gq subtype G-proteins together chimeric Gq α subunits.

In the past, activity of signal transduction mediated by GPCRs used to be assayed utilizing expression systems for cultured animal cells such as *Xenopus* oocytes. In such cases, however, assay methods had to be altered in accordance with the G-protein subtype that would naturally couple with a GPCR. In the assay system utilizing the *Xenopus* oocyte, for example, the GPCR that couples with the Gq subtype G-protein can be assayed by employing changes in Ca-dependent Cl current as an indicator. But the GPCR that couples with the Gi subtype G-protein cannot be assayed by Ca-dependent Cl response; it must be assayed by employing intracellular cAMP-dependent K channel activity as an indicator.

Nakamura deals with a system where it is possible to induce Ca-dependent Cl responses even without coexpressing the chimeric Gq α subunit because mGluR1 can couple with Gq subtype G-proteins (e.g., G_{L2 α}) and activate endogenous responses. See Nakamura, for example, Figures 2-4. In contrast, the present invention concerns expression of GPCRs that couple with G-proteins other than Gq subtype G-proteins together with a chimeric Gq α subunit by which it is possible to induce Ca-dependent Cl responses. Such responses cannot be induced without coexpressing the chimeric Gq α subunit.

Accordingly, there is no suggestion or motivation, either in the Nakamura reference or in the knowledge generally available to one of ordinary skill in the art at the time the instant application was filed to arrive at the claimed invention. If the Examiner is aware of

references which would tend to remedy these shortcomings of Nakamura, the Examiner is asked to cite them. If such facts are within the Examiner's personal knowledge, the Examiner is requested to make them part of the record by way of affidavit as required by 37 C.F.R. §1.104(d)(2). In the absence of such additional disclosures, the rejection under §103 cannot stand. Reconsideration is respectfully requested.

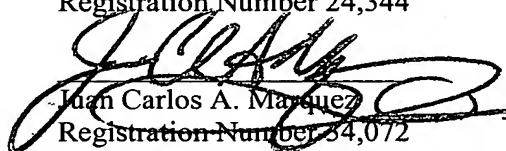
Conclusion

For the reasons presented above, all the claims pending in the application are believed by Applicant to define patentable subject matter and should be passed to issue at the earliest possible time. A Notice of Allowance is requested.

If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,

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